Clinico-Pathological Features in Young Patients with Rectal Cancer and the Influence of Clinical, Histological and Treatment-related Factors on Survival

Dr. Deepak Damodaran

This dissertation is submitted to The Tamil Nadu Dr. MGR University in partial fulfillment of the requirements for the degree of MCh (Branch VII) in Surgical Oncology

College of Oncological Sciences

Cancer Institute (WIA),

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Chennai – 600 020

August 2014

CERTIFICATE

I hereby certify that this dissertation on **"**Clinico-Pathological Features in Young Patients with Rectal Cancer and the Influence of Clinical, Histological and Treatment-related Factors on Survival**"** is a bonafide work done by **Dr. Deepak Damodaran** in the department of Surgical Oncology, College of Oncological sciences, Cancer Institute (WIA), Chennai, under my guidance and supervision, to my satisfaction.

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CERTIFICATE

This is to certify that the dissertation entitled “Clinico-Pathological Features in Young Patients with Rectal Cancer and the Influence of Clinical, Histological and Treatment-related Factors on Survival” is a bonafide work done by **DR. Deepak Damodaran** in the Department of Surgical Oncology, College of Oncological sciences, Cancer Institute (WIA), Chennai in partial fulfillment of the University rules and regulations for award of MCh surgical oncology under my guidance and supervision during the academic year 2011 to 2014.

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CONTENTS

1. Introduction

Rectal cancer has in general been a disease of the middle aged and elderly, such that the most patients diagnosed with the disease are beyond 55 years of age. While only 2-10% of all rectal cancers in Western nations occur in young patients, it has been reported to occur with a much greater incidence among young patients in South East Asia [1]. At the same time, a recent population based study in the United States has reported an increasing incidence of rectal cancer in the young adults [2]. A number of recent epidemiologic studies have also highlighted such increase in the occurence of young-onset rectal cancer[3-7]. The cut off age or age group for defining patients with young rectal cancer with respect to aggressive biology and survival statistics is not well defined. There are studies citing 35, 40, 45and 50 years as the cut off ages with conflicting data with respect to poorer survival .In spite of its rising incidence, there are only a few studies on the prognosis and clinicopathologic features young-onset rectal cancer. Furthermore, it has also been observed that the survival of younger patients with rectal cancer is poorer compared to older patients [8]. While most agree that younger patients are diagnosed at

an advanced stage of the disease as compared with the older patients [9-11], and with poorer differentiation [12] resulting in poorer survival, it has also been suggested that the tumours in younger patients are biologically different to that in the older patients. Despite such differences in the tumor development and differentiation, patients with young-onset rectal cancer are currently being treated with similar procedure as later-onset ones and new treatment stratergies focusing on rectal cancer in young adults need to be developed [13,14In this regard, there have been conflicting data from studies of Western patients with some reports suggesting a poorer outcome for younger patients [15,16], while others indicate no difference in the stage-specific oncologic outcomes between the young and older cohorts [17]. Therefore, in this thesis we present a systematic study of rectal cancer in young adults and survival outcomes in young rectal patients in the southern parts of India as compared to their older counterparts. The central goal of this work is to analyse the relative distribution and the clinicopathological profile of rectal cancer across various age groups especially among the young. At the same time, we analyze and compare the effectiveness of treatments towards the outcomes

between the younger and older patients with the future goal of tailoring treatment strategies which could account for the differences in the biological features of rectal cancer in younger patients.

2. Review of Literature

Colorectal Cancer (CRC) is a major cause of morbiditiy and mortality globally resulting in more than 500,000 deaths anually) [18]. More than 90% of the patients with CRC in the West are diagnosed post55 years of age and is hence considered primarily to be the disease of the elderly. Consequently, in the absence of predisposing conditions like idiopathic inflammatory disease (IBD) or familial syndromes, screening programs for rectal cancer usually start at the age of 50 years [19]. While the estimated incidence of rectal cancer in India (2.0–3.3 per 100,000 population in men and 1.4–2.4 per 100,000 in women) is much lower than Western countries (12.9–18.8 per 100,000 in men and 6.9–8.6 per 100,000 in women in the United Kingdom) [20]; there have been speculations that there might be a high relative incidence of rectal cancer amongst young South-East Asian populations [21,22]. The Madras Metropolitan Tumour Registry (MMTR), a population based cancer registry in Chennai shows a crude incidence rate of 4.4 /1,00,000 for rectal cancer in males with an age specific rate of 4.8/1,00,000 during the year 2009-2010.

In a recent study involving 89 adult patients diagnosed with rectal cancer from North India, it was shown that the average age of presentation was found to be as low as 45 years [23]. Moreover, studies based on the hospital registry at the Christian Medical College, Vellore demonstrated that the relative incidence of rectal cancer in the age group 40 years and younger can be as high as 35.5% [24]. The same was observed in yet another study from Maulana Azad Medical college, New Delhi that focussed exclusively on rectal cancer in the age group from 10-25 years and reported 32 patients in this group with an incidence of 9.9% of the total colorectal cases registered [25].

Apart from the high occurence of young rectal cancer in India as reported above, the studies from CMC, Vellore [24] also suggested that the histopathological features of rectal tumours in young Indian patients under investigation were in agreement with similar studies in West. In their study, it was found that young patients undergoing surgery had a higher chance of receiving neoadjuvant therapy because of more advanced disease at presentation. Despite the possible downstaging effects of such therapy, young patients

undergoing surgery had a more advanced pathological T and N stage compared with the older group. The more advanced histopathology seen in young patients in this study are in accordance with several other studies involving western patients [26].

Another study from Tata Memorial Centre, further showed that the younger patients had higher stage at diagnosis with higher lymph node positivity and lower Disease Free Survival (DFS) [27]. They reported a significantly poorer stage-specific DFS with stage III disease in patients less than 40 years of age as compared to the older patients. Their findings concurred with those of Smith et al. [16] and Cusack et al. [15] and contradicted reports that attributed the poorer survival in younger patients to delays in presentation with no difference in stage-specific survival between old and young rectal cancer patients [17, 28]. While the lack of screening and symtoms being overlooked that occurs in the case of younger patients is an important factor for the poorer survival statistics that has been seen in younger patients as compared to their older cohorts (3),(7N), this by itself does not explain the mucinous prevalence and poor differentiation in young rectal cancer and the fact that the tumour

location has been found to vary with patient age [29]. Furthermore, researchers have observed different time trends in the occurence for subsites and genders for rectal cancer in young adults suggesting different etiology in them as compared to older patients [30, 31]. The current opinion regarding the relatively lower survival in younger patients is trending to the fact that while the biology of rectal cancer is different than in older patients, the diagnosis, screening and treatment strategies remain the same and are not tailored to account for these differences [32]. A better understanding of the biology of rectal cancer and etiological factors including gentics, histology, environmental factors and others, are necessary for developing effective diagnosis, screening and treatment strategies for rectal cancer in young adults.

2.1 Role of Genetics

Despite several studies on the etilogical factors for rectal cancer in young adults, it is still unclear as to why young adults without a predisposing genetic abnormality develop rectal cancer? It has been reported previously that only a small minority can be linked to known predisposing syndromes, including familial polyposis syndromes, hereditary nonpolyposis colorectal cancer (HNPCC) or the Lynch syndrome, inflammatory bowel disease and more [2]. Moreover, established pathways of carcinogenesis in rectal cancer, such as chromosomal instability/aneuploidy, microsatellite instability, APC-mutation, KRAS-mutation account only for small subsets of young patients [10, 33-35]. It may be hypothesized that even after exclusion of all patients with known HNPCC, a significant subset may possess undiagnosed HNPCC. If this were true, the incidence of microsatellite-high (MSI-high) rectal cancer would be expected to be low. While a recent population based study of patients with rectal cancers revealed that MSI-high status was found in only 2.2% of the cases; another study enriched with patients younger than 50 years found MSI-high status in 17% of the tumours [28]. Several studies have also proposed

that chromosome 14 can play an important role in microsatellite stable colon carcinogenesis. As loss of chromosome 14 is more frequent in aggressive tumours and in young patients, this gene location is probably responsible in part for tumour aggressiveness and hereditary predisposition as reported by Mourra et al. [36]. Furthermore, Dunlop et al. [37] and Phillip et al. [38] also described microsatellite instability as the cause for underlying tumour development in young CRC patients, regardless of HNPCC status [39]. The majority of these studies, however, suggest only a minor role of genetics towards the etiology for rectal cancer in the majority of the young patients.

2.2 Patterns in Histopathological Types

Several studies have shown that the pattern of histopathological types of rectal cancer differs in younger age patients as compared to their older cohorts. An article in Nature, reviewing the biology of cancer in young adults, reported that Mucinous adenocarcinoma occurs in nearly 50% of the cases for young adults as compared to only 2–4% in older adults [32] and are associated with a worse prognosis. Griffin et al. [40] reported that ~28% of the lesions found in younger patients was constituted by mucinous tumours compared with ~5% for older cohorts. Further, mucinous adenocarcinoma showed higher frequencies of poor differentiation, advanced tumour stage, loss of MMR expression, and increased MUC2 expression compared with non-mucinous adenocarcinoma. The worse outcome in young patients has been attributed to the high percentage of this histologic subtype and of poorly differentiated tumours found in the age category [41].

2.2 Impact of Environmental Factors

It is thought that environmental factors, especially dietary habits, can contribute to the increasing incidence and geographic distribution of rectal cancer. An empirical proof that has been provided for this is the westernization of the diet in Japan, which following 15 years of changed dietary behaviourhas become a high-risk country for CRC[2]. Similar observations have also been made on Japanese immigrants to the United Staes [8] who adopted American culinary habits.

3. Modalities in the Treatment of Rectal Cancer

3.1 Work up

The standard work up for rectal cancer entails a history, physical examination, complete blood cell count, liver and renal function studies, as well as carcinoembryonic antigen (CEA) evaluation. High CEA levels are linked with poorchances of survival and indicate as to whether follow-up CEA determinations wouldbe useful. A careful rectal examination by an experienced examiner is an essential part of the pretherapy evaluation in determining distance of the tumour from the anal verge or from the dentate line, involvement of the anal sphincter, amount of circumferential involvement, clinical fixation, sphincter tone, and has not been replaced by imaging studies or endoscopy. Colonoscopy or barium enema to evaluate the remainder of the large bowel is essential (if the patient is not obstructed) to rule out synchronous tumours or the presence of polyp syndromes.

3.2 Histopathology

The commonest histological type of rectal cancer is adenocarcinoma. Other histology types like squamous cell carcinoma, melanoma, neuroendocrine carcinoma, GIST were excluded. Among the adenocarcinomas, numerous histologic types of CRCs carry specific independent prognostic significance. For example, signet ring carcinomas are characterized by more than 50% of cells demonstrating the signet ring cell type morphology in which intracellular mucin accumulation displaces the nuclei and cytoplasm toward the cellular periphery. This histology carries an adverse prognosis [43]. The prognostic significance of the finding of mucinous carcinoma (more than 50% mucinous component) remains contentious. Although some reports list mucinous type as an adverse histology, this observation has not been consistent.

3.3 Clinicopathological Staging

Standard clinicopathological staging is the best indicator of prognosis for patients with rectal cancer. For rectal cancer, it is increasingly common to use clinical staging and imaging in combination as the basis for the decision for neoadjuvant chemoradiation therapy. Therefore, the accuracy of that initial staging is critically important, both for management and for prognosis.

3.3.1 AJCC 7th edition staging and stage groupings

Patients have both a clinical (preoperative) staging, which may define the use of neoadjuvant therapy, and a postoperative surgical stage [44]. However, the initial therapy with radiation and chemotherapy can produce substantial down-staging (approximately 15% of patients will have a pathological complete response), and that subsequent therapy should be based on the initial T and N staging determination. Even with a good tumour response locally in a patient who receives preoperative radiation and chemotherapy, postoperative chemotherapy should be given irrespective of the surgical pathology result. Until the data demonstrate otherwise, the plan for postoperative chemotherapy should be carried out even in the setting of a

pathological complete response. The major change that has occurred in the newest version of the staging system is the acknowledgment that both the T stage and the N stage have independent prognostic importance for local control, disease-free survival, and overall survival [25, 27]. Thus, for N0 and N1 patients viewed separately, the extent of the primary tumour in the rectum is of additional prognostic importance. Patients with T1-2N1 tumours have a relatively favorable prognosis and an outcome superior to that of other stage III patients. In fact, patients with T3N0M0 disease (stage II) have outcomes slightly inferior to those with T1-2N1M0, demonstrating the

Primary Tumor (T)		Regional Lymph Nodes (N)		Distant Metastases (M)	
Tx	Primary tumor cannot be assessed	NX	Nodes cannot be assessed (eg, none in specimen)	MX	Presence of distant metastases cannot be assessed
T0	No evidence of tumor in resected specimen (prior polypectomy or fulguration)	N0	No regional node metastases	M0	No distant metastases
Tis	Carcinoma in situ	N1	1–3 positive nodes	M1	Distant metastases present
T1	Invades submucosa	N2	4 or more positive nodes		
T2	Invades muscularis propria				
T3–4	T3 invades through muscularis propria into subserosa or into nonperitonealized pericolic or perirectal tissue T4 invades into adjacent organs or tissues and/or perforates visceral peritoneum				

Stage	TNM
0	Tis N0 M0
I	T1 N0 M0, T2 N0 M0
IIA	T3 N0 M0
IIB	T4 N0 M0
IIIA	T1 or T2 N1 M0
IIIB	T3 or T4 N1 M0
IIIC	Any N2 M0
IV	Any T any N M1

Table 1: AJCC7 Staging System for Colorectal Cancer [44]

independent prognostic importance of T stage. Although, at one level staging is very straightforward, the actuality of proper staging is much more difficult as it relies on multiple quality control issues that can mislead the clinician regarding proper therapy. The vital components of staging are-

- Experienced clinical staging
- Quality in terms of imaging for T stage , Nodal (N) stage , Mesorectal fascia
- Pathologic asseessment in terms of completeness and grade of Total Mesorectal Excision(TME), nodal yield, Circumferential radial margin(CRM)

3.4 Treatment of Rectal Cancer at Cancer Institute (WIA).

3.4.1 Neoadjuvant Therapy

Neoadjuvant therapy consisted of 2 cycles of intravenous 5 fluorouracil at a dose 325mg/m^2/day for 5 days (concurrently with radiation) and 1 cycle of Mitomycin C at a dose 6 mg/sq.m for 1 day (concurrently with radiation). External beam irradiation was administered up to a total dose of 5000 cGy (25 fractions, 200 cGy per fraction) administered by a four field box technique over a period of five weeks. The field included the tumour site within the pelvis as well as the lymphatic draining area reaching up to the L-5 to S-1 superiorly and the ischial tuberosities inferiorly. Laterally, the radiation field extended 1.5 cm beyond the bony pelvis. On the posterior aspect, the radiation encompassed the entire sacrum.

3.4.2 Response to Treatment

Patients were restaged at four weeks after completion of NCRT to evaluate tumour response. Tumour response assessment consisted of similar radiologic and clinical studies used at initial staging. Clinical response to neoadjuvant chemoradiation was judged on surface area

of abnormality (tumour size) and intramural involvement (induration). Clinical response was defined as per following:

- **Complete**: No residual tumour, no surface abnormality, no induration.
- **Partial**: more than 25% reduction in surface abnormality and induration.
- **Stable**: No change in surface abnormality and induration.
- **Progression**: progression of disaese local/syatemic during neoadjuvant treatment

3.4.3 Surgery

Surgery was performed at 4 to 6 weeks after completion of NCRT. Surgery consisted of a total mesorectal excision (TME) based resection, either abdominoperineal resection or low anterior resection with en bloc resection of any adjacent organ involvement. Lymph nodes up to the origin of the inferior mesenteric artery are harvested.

3.4.4 Pathologic assessment

All the surgical specimens were fixed in 10% (by volume) formalin and routinely processed for paraffin embedding. Lymph nodes were

retrieved via gross examination and manual palpation. Patients were staged according to the American Joint Committee on Cancer guidelines (AJCC) [42]. Pathology reports included tumour size in cm, histology type, pathology stage, total number of regional lymph nodes present in the resected specimen, and number of lymph nodes with cancerous cells, and circumferential radial margin (CRM) and proximal and distal margins.

4. Aims and Objectives

The following are the aims and objectives of my thesis:

a) To determine the relative distribution and the clinicopathological profile of rectal cancer across various age groups especially among the young

b) To study the influence of clinical ,histological and treatment related factors on survival

c) To determine if possible any age cutoff defining young rectal cancer which would show a survival difference over the older cohort .

Selection Criteria

A) Inclusion criteria - All cases diagnosed with Carcinoma rectum from 1995 to 2007

B) Exclusion criteria – Histological types of tumour such as carcinoid, gastrointestinal, stromal and neuroendocrine tumours, melanoma, squamous cell carcinoma were excluded.

Patients with Familial Adenomatous Polyposis or those with other confirmed familial carcinoma syndromes were excluded from the study.

5. Materials and Methods

A retrospective study of 552 patients, presenting to the Department of Surgical Oncology at Cancer Institute (WIA), Adyar, Chennai, India and registered in the tumour registry at the Institute between January 1998 and December 2007 was done. Only patients with histologically proven primary rectal adenocarcinoma were included, as defined as tumour involvement within 15 cm of the anal verge on digital rectal examination／colonoscopy and／or CT imaging. The tumor location was classified as follows: low rectum (0 to 6 cm from the anal verge), mid rectum (> 6 to 10 cm), and high rectum (more than 10 cm). Demographic data, presenting symptoms and their duration, pathological features of the tumour, tumour localization, histological data, pre-operative carcinoembryonic antigen (CEA) level, treatment modalities and survival data were retrospectively recorded and were analyzed.

Tumor staging was as per the AJCC standards performed at the same time period as the treatment . Clinical stage was determined by preoperative imaging and endoscopy, including computer tomography (CT). Pathologic stage was based on the surgical resection specimen.

Chemotherapy regimen was 5-fluorouracil based. Surgical treatment was broadly categorized as abdominal perineal resection (APR), low anterior resection (LAR), which included all sphincter-preserving operations (i.e. coloprocto- or coloanal anastomosis), anterior resection and exented extenteration surgeries with multiorgan resections.

Follow up was by direct communication with patients and their relatives in the out-patient clinic or by telephone or mail. Patients were considered lost to follow up if the patient had failed to present at an out-patient clinic, or could not be contacted by telephone or letter, after more than 3 years. During follow up, patients were assesed by history and physical examination, including digital rectal examination and CEA level every three months. A chest radiograph and trans-abdominal ultrasound scan or computerized tomogram was undertaken at one year. Colonoscopy was done once in five years. The date and site of the first tumour recurrence was reviewed. Recurrences were categorized as local if they were perianastomotic or located in the pelvis, and as distant if they involved para-aortic nodes,

liver, lung, or other distant organs. Patients were followed to their date of death or their last contact in the OPD.

Statistical Considerations

The estimated Statistical analysis will be done with SPSS software. Clinical profile and other variables will be carefully documented. Follow up details will be entered. Statistical correlation for multivariate analysis will be done with the help of cox regression method. Data were entered into Excel 2008 (Microsoft Corporation, Redmond, WA) and analyzed with SPSS® (SPSS Inc., version 8.0, Chicago, IL). $P \leq 0.05$ was considered statistically significant. The chi-squared test for trends or Fisher's exact test was used whenever required.

6. Results

6.1 Demography of patients

In our effort to analyze the clinicopathological data and survival outcomes across the age groups, we categorized for demographic stratification as patients into two groups - (1) less or equal to 40 and (2) more than 40 years. Also distribution patterns were studied across every 10 year age groups. Figure 1 shows the distribution of the 552 patients across the various age groups. 173 patients belonged to group 1 (less or equal to 40) thus constituting 31% of the study population. 13% were <30 and 52% were younger than 50. Thus more than 50% of our rectal cancers

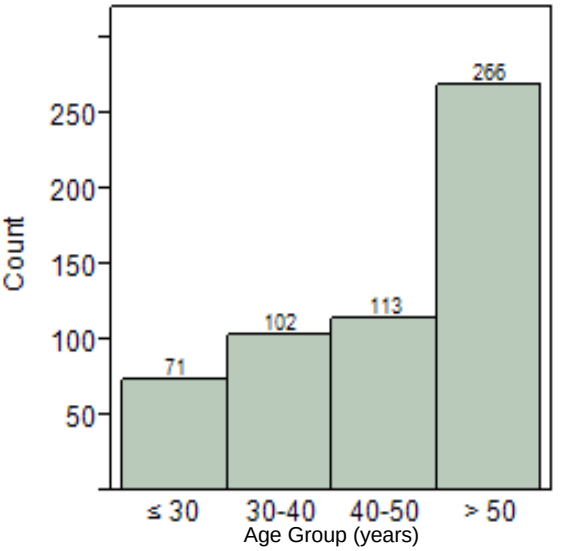

Fig. 1: Age distribution of patients studied

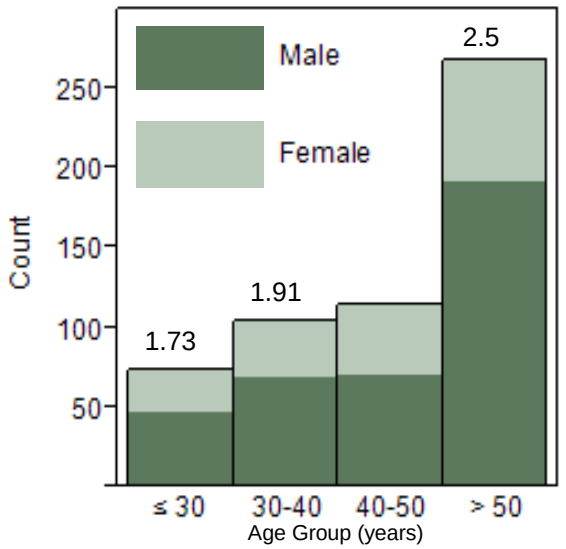

Fig. 2: Male to Female ratio of patients in each age group

patients are younger than 50 in contradiction to the western statistics. The reasons possibly being increased incidence of CRC in the young in our sample population and probably confounded by the fact that we have a demographically younger population compared to the West. The male/female ratio was statistically insignificant across age groups with a p value of 0.198 (Fig. 2).While 12 patients in group 1 had a family history of cancer as against 37 in group 2, the difference was insignificant with a p-value of 0.28 (Fig. 3). While familial colorectal syndromes like FAP and HNPCC were excluded from the

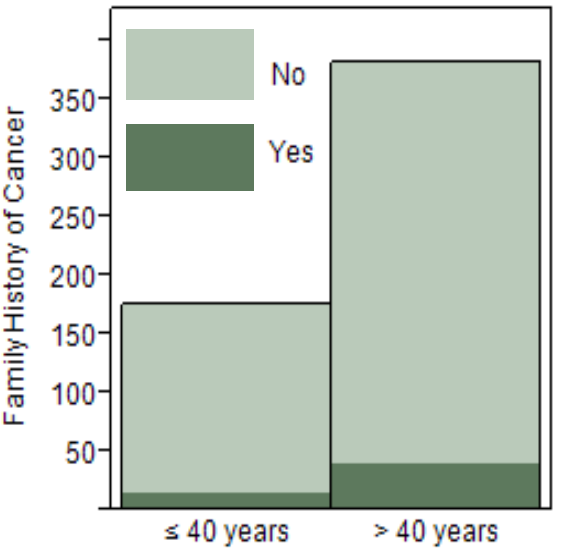

Fig. 3: Family history of cancer in 1.5 of each age group1.57

study, also few cases of ulcerative colitis with later development of rectal cancer were excluded. Nevertheless, the absence of any

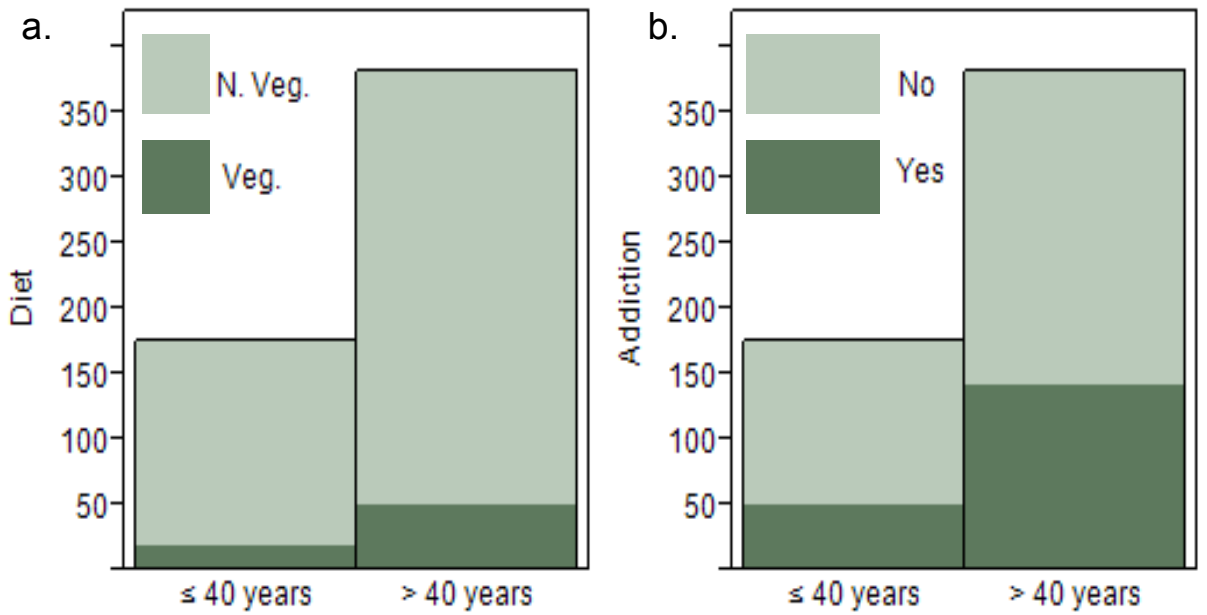

Fig. 4: Distribution of a) Dietary habits and b) Addition to alcohol, tobacco and others for patients in each age group

significant history of colorectal or any other malignancies in first degree relatives of the patients with respect to the older cohorts indicates that most of the cancers are possibly of sporadic nature. The pattern of dietary habits vegetarian vs non-vegetarian diet was evenly distributed among the population (fig. 4a). Addiction (alcohol, smoking and chewing tobacco, or a combination of any) showed up as a moderately significant factor for difference between the two age groups with p-value of 0.029* (Fig. 4b). However, addiction was significantly higher in the older age group and is therefore clearly not a

factor responsible for increasing incidences of young rectal cancer. In summary, we have not found any demographic factor to explain the increased incidence in sporadic rectal cancer among young patients as compared to that in older patients.

6.2 Clinical Features and Tumour Characteristics:

Clinical features of patients assessed were duration of symptoms, presence of comorbid illness and bowel obstruction. Fig 5 shows a significant proportion of the patients in group 1 with duration of symptoms (rectal bleeding) more than 6 months compared to the older

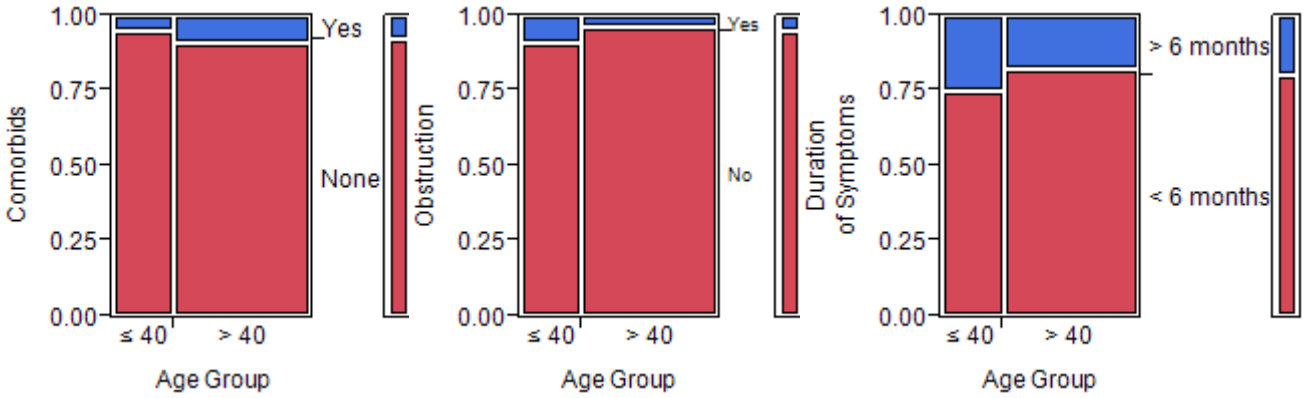

Figure 5: Contingency plots for normalized frequency of several clinical factors (comorbid, duration of symptoms, and obstruction) at the time of presentation

cohort. This may be possibly due to reluctance on the part of younger patients to consult physicians and may contribute to their advanced stage of presentation. The role of comorbidity that included pre-existing conditions like ischemic heart disease, chronic renal disease, COPD, liver disease which could compound the postoperative morbidity was found to be significantly greater in the case of older patients, as expected. Obstruction of bowel presented itself with

increasing incidence of 8.7% in young adults as compared to 3.4% in their older cohorts with the difference showing a moderately strong statistical significance with a p-value of 0.009*.Unlike left sided colonic cancers that have characteristically stenosing growth presenting with bowel obstruction, the rectum being voluminous due to its storage capacity rarely presents with bowel obstruction. The most common clinical symptom for rectal cancer is bleeding *per* rectum. Stenosing tumours presenting with bowel obstruction and hence requiring diversion colostomy before or during neoadjuvant treatment was found to be significantly higher in young adult patients. The presence of synchronous proximal polyps was found to be not statistically significant in the two age categories with a p-value of 0.175. The mean distance of tumour from the anal verge was found to have a rising trend as evident in Fig 6 i.e. higher age further is the tumor from the anal verge .The median distance of

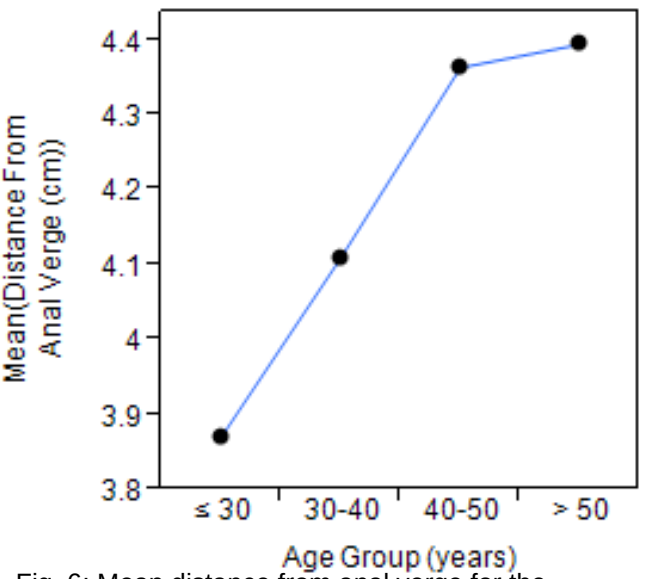

Fig. 6: Mean distance from anal verge for the different age categories

tumor from the anal verge was 4 cm across all age groups. Around 81.5% of the tumours were within 6 cm from the anal verge (distal rectal cancer), with incidence varying from 85.5% in group 1 to 79.7% in group 2. The distance was categorized to three levels: '**1**' for distance less than 6 cm,(low rectum) '**2**' for values more than 6 up to 10 cm (mid-rectum); and '**3**' for distances greater than 10 cm (high rectum) for analysis of statistical significance and yielded a p-value of 0.137 indicating no significance. The median CEA values at presentation/diagnosis are higher in the younger populations, though not statistically significant as shown in Fig. 7. Statistical studies for difference in the incidence of circumferential and fixed tumours among young and old patients showed an extremely strong significance with a p-value of less than 0.0001*.

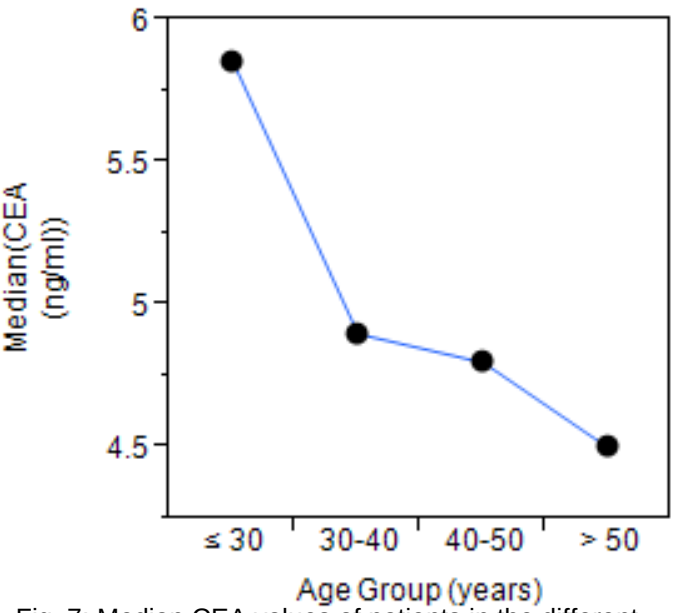

Fig. 7: Median CEA values of patients in the different age categories

Circumferential and fixed tumours by merit of their infiltrative growth pattern and probably the duration involved in tumour progression are inherently more aggressive in behavior compared to the polypoidal non-circumferential growth. In fact, most of the young adult patients (~71%) had circumferential tumours as compared to the 50% incidence of circumferential tumours in the older cohorts (Fig. 8). In addition to this, Fig. 9a shows that about 68.5% of the tumours in young adults are fixed compared to 46.7% in the older cohorts. To further understand the trend in fixed tumours with age we look at the

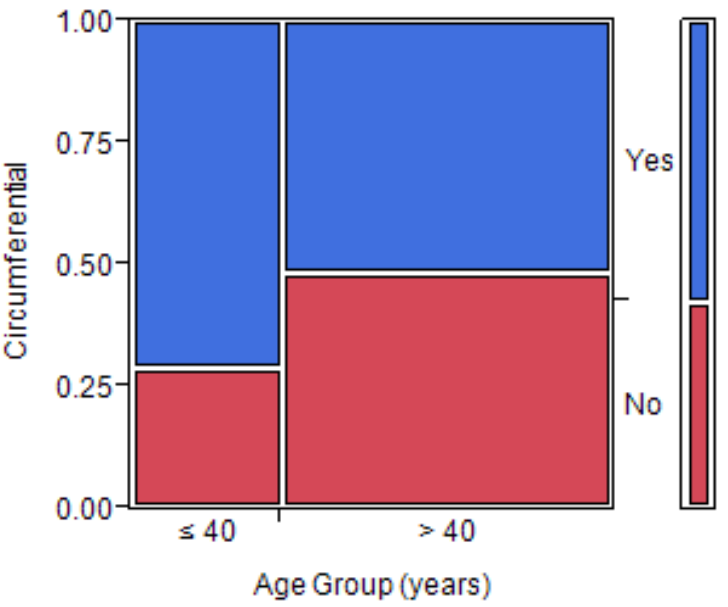

Fig. 8: Contingency plots for normalized frequency of circumferential tumour

trend in four different age groups as in Fig. 9b and observe that the incidence of rectal cancer with fixed tumour is inversely related to the age of the patient. The statistical study reveals a strong significance with a p-value of less than 0.0001* and lead us to conclude that the incidence of circumferential and fixed tumours are much higher in

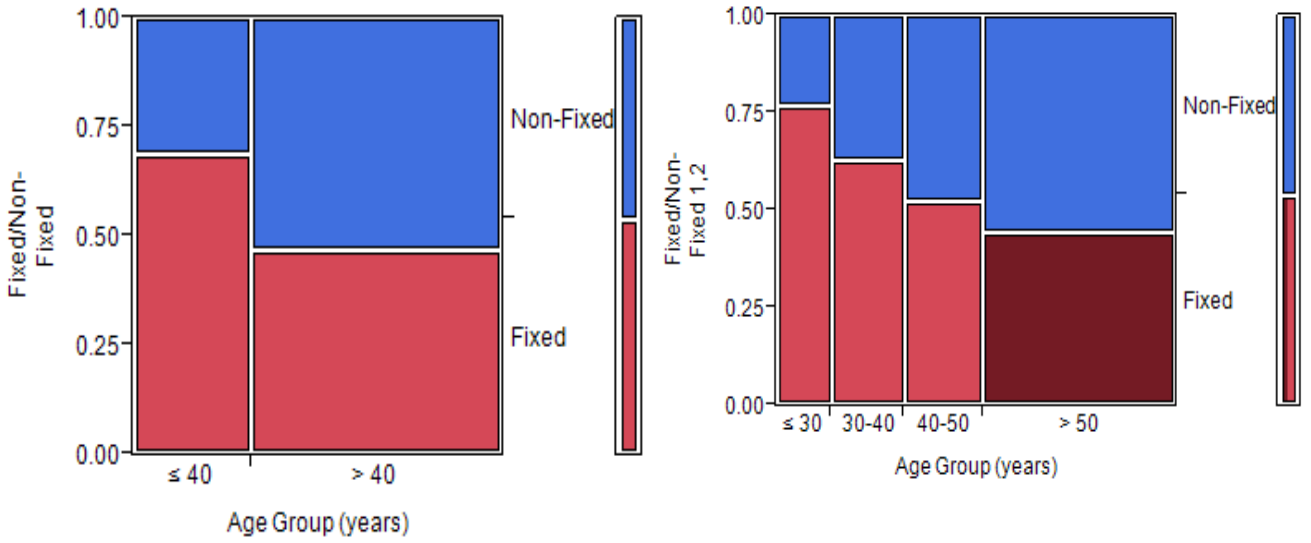

Fig. 9: Contingency plots for normalized frequency of fixed tumour in the age categories a) less than and greater than 40 years old and b) for the categories < 30, 30–40, 40-50, >50

younger patients and suggests aggressive infiltrative growth pattern of rectal cancer in younger adults.

6.3 Grade of Tumour (Tumour Differentiation)

The grade of the tumour (tumour differentiation) was compared across the age groups and has been summarized in Fig. 10. While the number of well differentiated tumors were 6 and 8% in groups 1 and 2 respectively, the number of poorly-differentiated ones were 50% in group 1 as compared to 31.5% in older patients (group 2) showing a high statistical significane with a p-value of less than 0.0005*. The

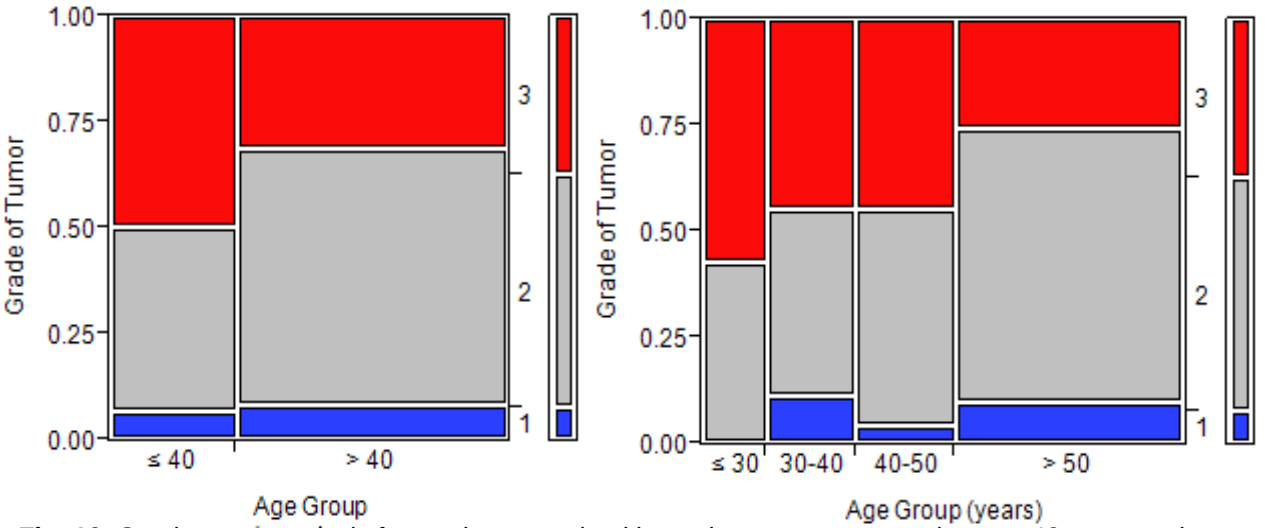

Fig. 10: Contingency analysis for grade categorized by patient age group as a) < or > 40 years and b)<30, 30-45, 45-60 and > 60 categories

findings here are in tune with several other reports of poorer tumour differentiation in younger adults. The trends shown in Fig. 10 also indicates that the number of poorly-differentiated tumours is inversely proportional to patient age (p-0.0001*).

6.4 Histology

Tumour histology was compared across the age groups and has been summarized in Fig. 11a. The histology was broadly categorized into 1) Adenocarcinoma, 2) Signet Type Ring, and 3) Others including Mucinous Adenocarcinoma. Conventional adenocarcinoma was predominant across both the age groups with higher proportions in the older cohort. Analysis of distribution of tumour histology gave a p-value of <0.0001* indicating high statistical significance. The higher grade signet ring histology were in significantly higher proportions in the young as has been previously reported. In order to gain additional insight we looked for statistical significance for incidence in each age

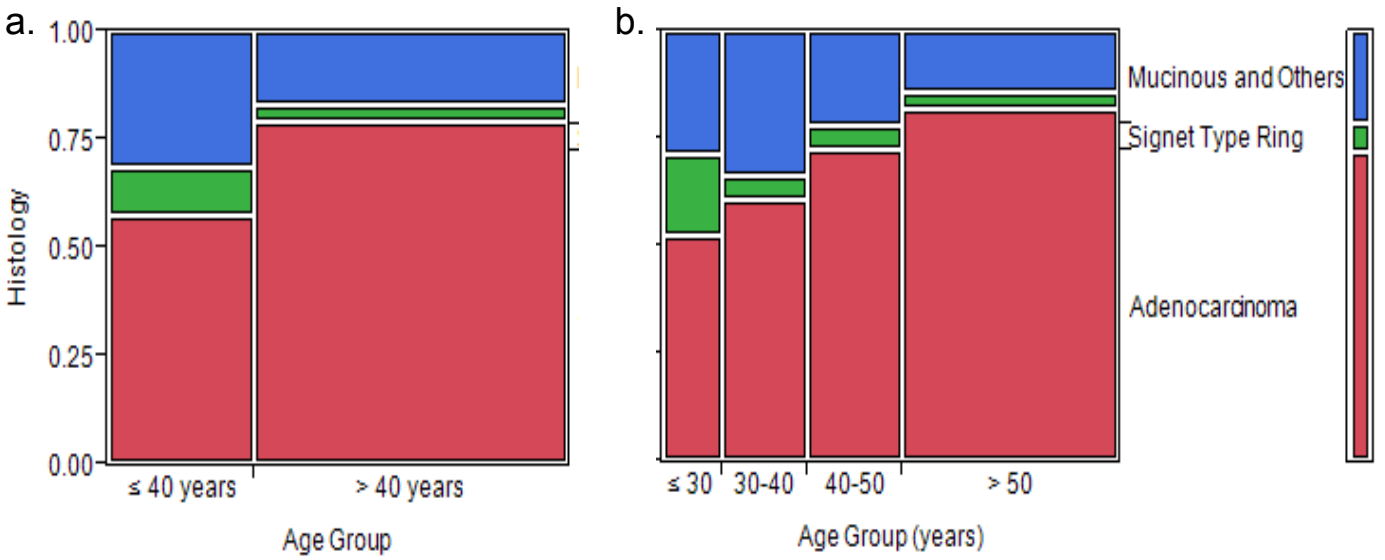

Fig.11: Contingency analysis for histology categorized by patient age group

category (**Fi**g 11b). Again we see that the incidences of adenocarcinoma was higher in older patients and was found to have a high statistical significance of less than 0.0001*. An interesting difference, however, has emerged in this study is that while the incidence of mucinous adenocarcinoma is uniform across the ages in patients younger than 50 years, the incidence of signet type ring is mostly restricted to patients less than 30 years of age.

6.5 Clinical Staging of Patients

The Fig.12 shows the normalized frequency comparison for the clinical T stage (cT) for the two age groups. Younger patients present with an overal higher cT stage than the older cohort with significance of $p < 0.0001$*. 26% of the young had cT4 stage compared to 10% in the old. While 58 of the 552 cases had synchronous metastasis and their distribution among the young (12.7%) and old (9.5%) was satistically insignificant.

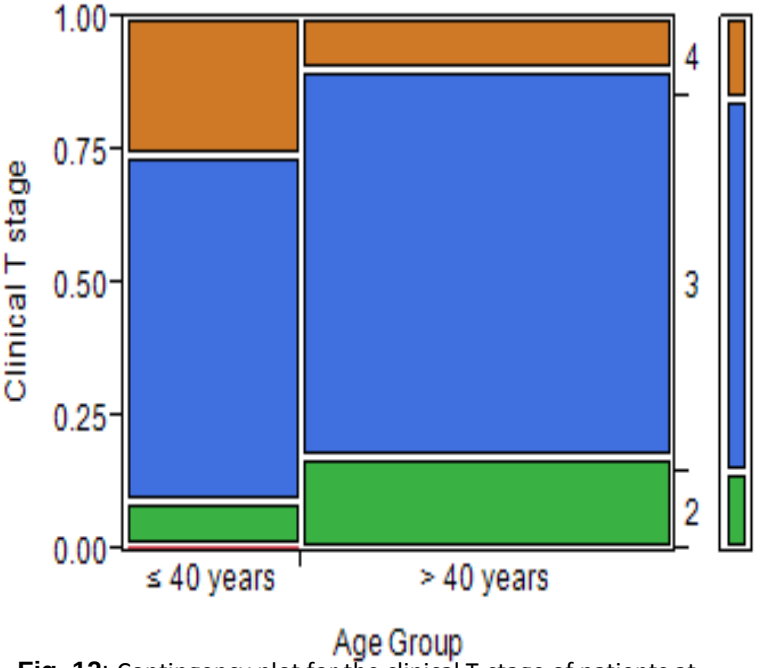

Fig. 12: Contingency plot for the clinical T-stage of patients at presentation

For completeness, we note that, during the period of study from 1998-2007, there were 779 cases that had reported to the Out Patient Department of the Cancer Research Institute, but were not evaluated because of distant metastases or locally advanced stage of cancer. Of these, 185 patients were less than 40 years as compared to 594 patients who

were older than 40. If these cases were to be included to the 532 cases that were evaluated during the same time period, 23.2% of patients younger than 40 were diagonosed with distant metastases as compared to 22.6% patients in the older cohort. Fig.13 shows the contingency plot for this distribution and yields a statistically insignificant p-value of 0.825.

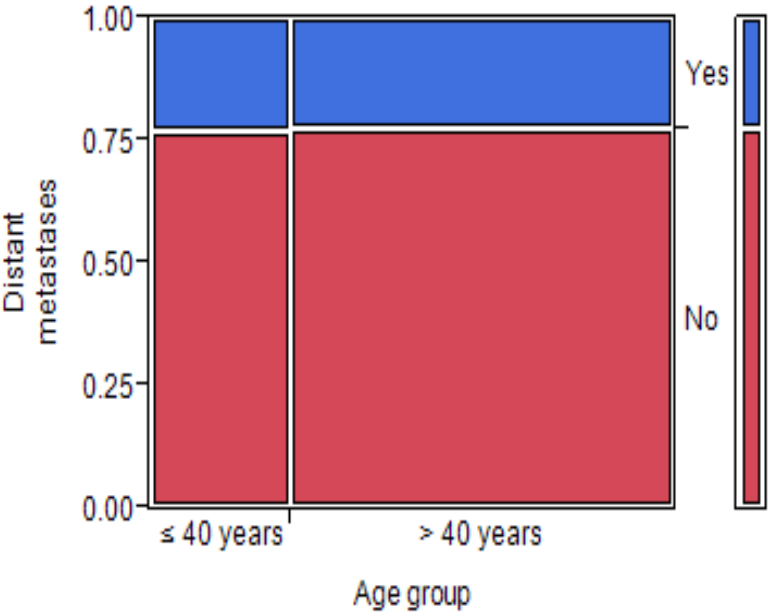

Fig. 13: Contingency plot for patients diagnosed with distant metastases at presentation

6.6 Neoadjuvant Therapy and Clinical Response

More patients in the younger cohort were directed to NACT and RT (Fig. 14a) due to higher clinical stage at diagnosis, as seen in the earlier section, compared to the old. This difference, however, on analysis was found not to be statistically significant (p=0.062). Fig. 14b shows the contingency plots comparing the clinical response for patients undergoing neoadjuvant treatment in the age categories under study. The clinical response was classified as complete, partial, stable and progression. As seen in the figure;

26 patients of the 385 patients who received NACT RT had clinical

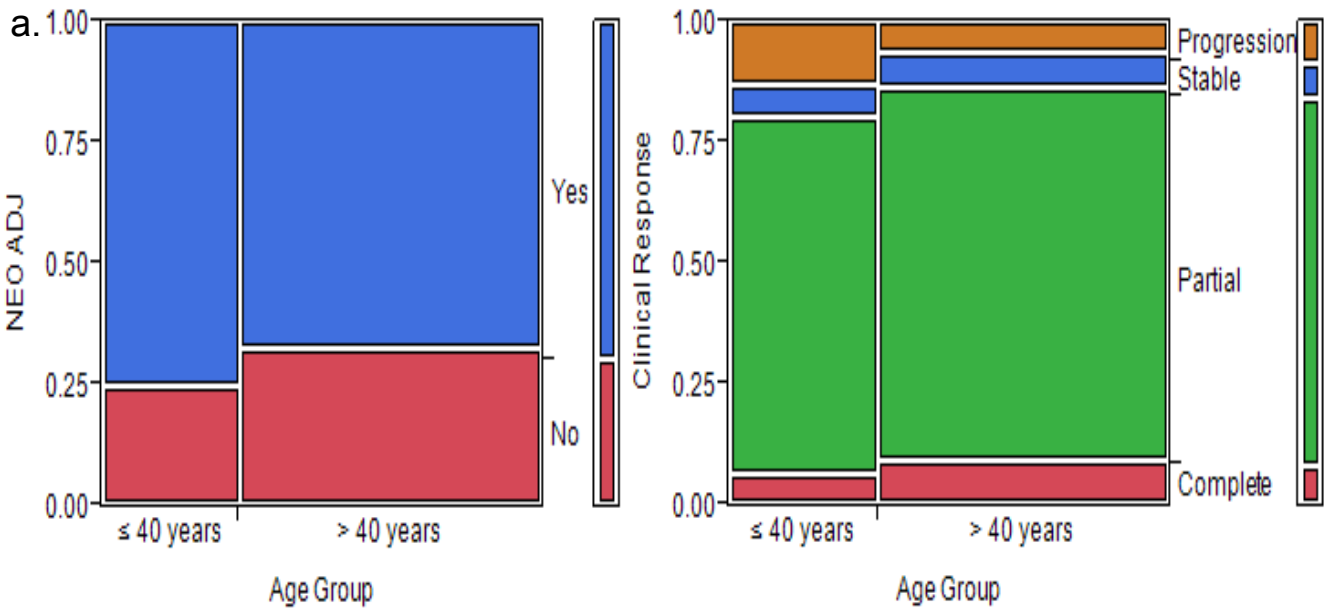

Fig. 14: Contingency plots for a) patients receiving neoadjuvant treatment and b) their clinical respons for the respective age categories

complete response; 7 in the younger group and 19 in the older cohort (NS). At the same time, disease progression was more frequent in the younger patients (13.1%) as compared to the older patients (6.3%). These differences in the overall clinical response to NACT and RT in the two groups yielded an insignificant p-value of 0.207.

6.7 Type of surgery and pathological staging

The type of surgical treatment was broadly grouped as abdominoperineal resections (APR), sphincter preserving surgeries which would include low anterior resection (LAR) and anterior resection (AR) and others. As is seen in Fig.15 the most common surgery done was APR which is evident from the analysis of distance of tumor from the anal verge showing most tumors being within 5 cm. There is no statistical significance (p=0.473) in the type of surgery in the young and old in the two age groups.

On analysis of the data with respect to the number of sphincter sparing surgeries, it is observed that sphincter preservation surgery was more commonly performed during the latter half of the study from 2003 – 2007 compared to the initial five years. This is possibly due to

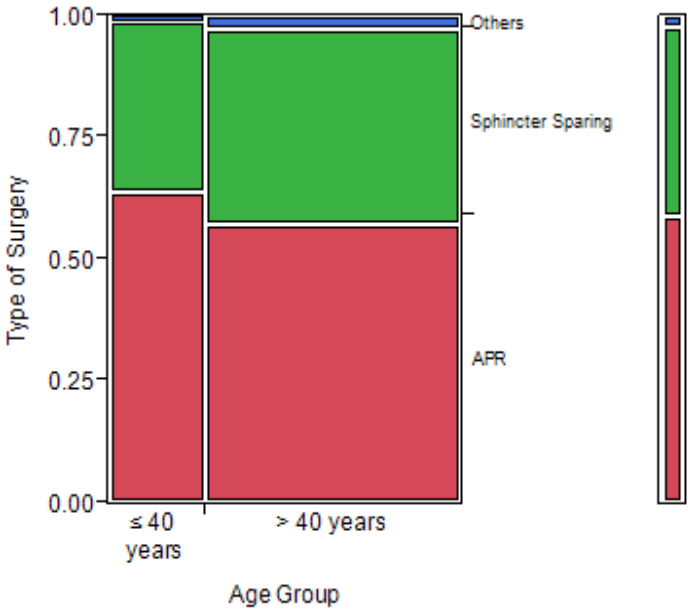

Fig. 15: Contingency plots comparing types of surgery across age groups

the distal resection margin up to 1cm being oncologically safe, becoming acceptable in the last decade and with better available surgical techniques more sphincter preservation surgeries were possible with distal tumors. Among the patients who underwent surgery, 91 had straight surgery by virtue of higher tumors and early stage at presentation and 229 had surgery after neoadjuvant therapy. The pathological T and N stage for these two groups were analyzed separately. For patients undergoing direct surgery, Fig. 16 shows a significant higher pT stage in younger patients undergoing straight surgery (p-value =0.001*) and no statistical significance in the pN

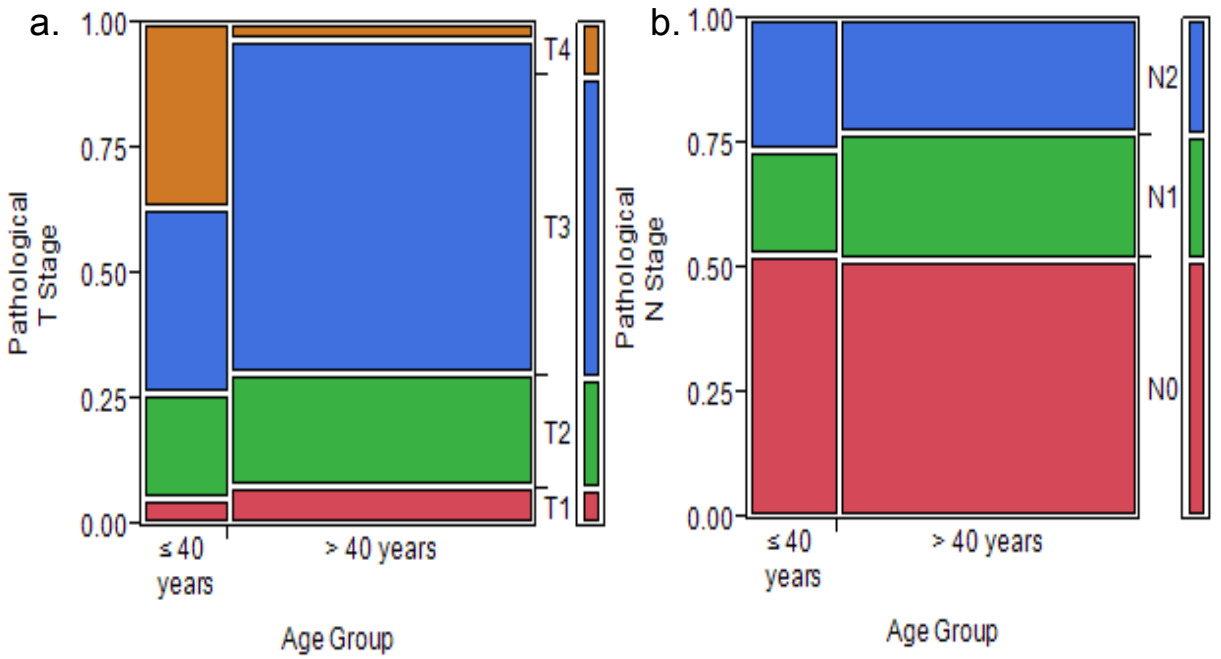

Fig. 16: Contingency plots of normalized frequency for a) the pathological T stage and, b) the pathological N stage respectively for patients that underwent direct surgery

stage (p-value=0.88).

Among patients who underwent surgery after downstaging (Fig. 17), the ypT stage among the groups was not significant (Fig. 17a), but the ypN stage assumed significance with a p value of 0.003* (Fig.17b). However this was not reflected in the final AJCC staging with 5.2%, 21.5%, 46.4% and 9.2% of the patients over 40 years categorized as

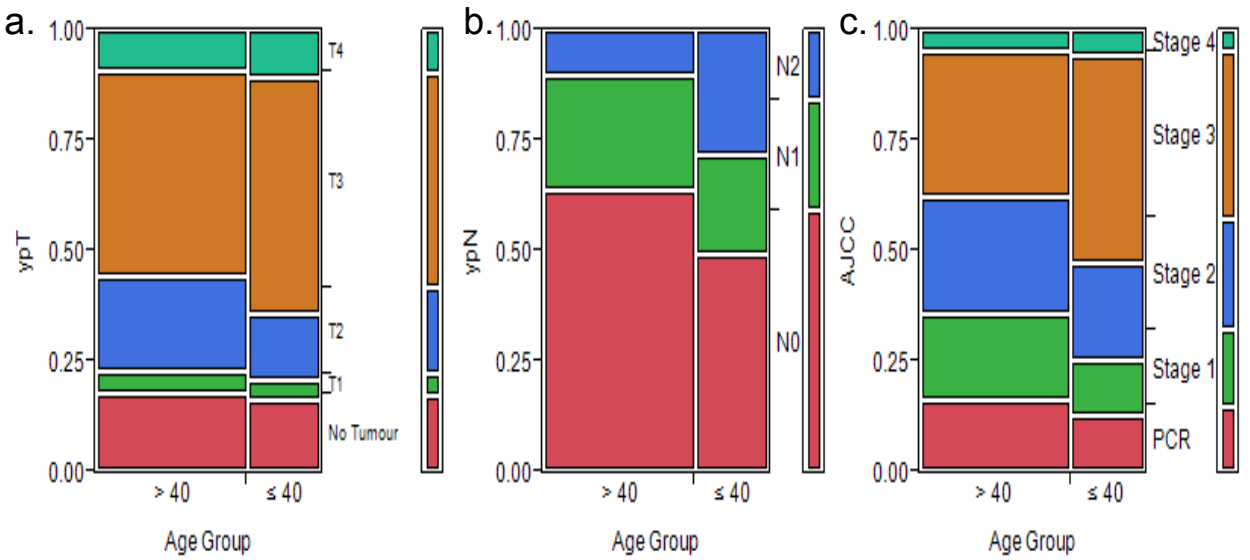

Fig. 17: Contingency plots of normalized frequency for a) the ypT stage, b) the ypN stage and, c)the AJCC stage for patients that underwent neoadjuvant treatment and surgery

stage I, II, III and IV respectively and in comparison to 4.1%, 15.1%, 53.4 and 11.0% in the younger group (Fig. 17c). While the distribution of patients as per the AJCC staging was similar in young and older patients, the number of positive nodes harvested was significantly

higher in younger patients (15.6% with >3 positive nodes harvested), i.e. higher percentage of N2 disease, as compared to the older cohorts (8.7%) with a p-value of 0.016*. The median number of lymph nodes harvested in the younger group was 10 and those among the older was 7. The median pathologically positive nodes retrieved in the younger group was 4 and in the older group was 3 nodes. Of the patients who underwent curative surgery there were 35 patients with complete pathological response. This consisted of 10 younger and 25 older patients and as seen in Fig. 17c comprising of about 11% of the total candidates that underwent surgery and is similar across of the two age groups in spite of the more aggressive form of the disease in younger patients. (the numbers being very small, hence no statistical analysis deemed worthwhile).

The cases of recurrence following surgery was also similar in the two groups (Fig. 18a) the difference was statistically insignificant with a p-value of 0.52. The recurrence rates were 28.5% and 25.7% in the younger and older patients respectively. The local recurrence rates were more frequent in the young and this trend towards higher local

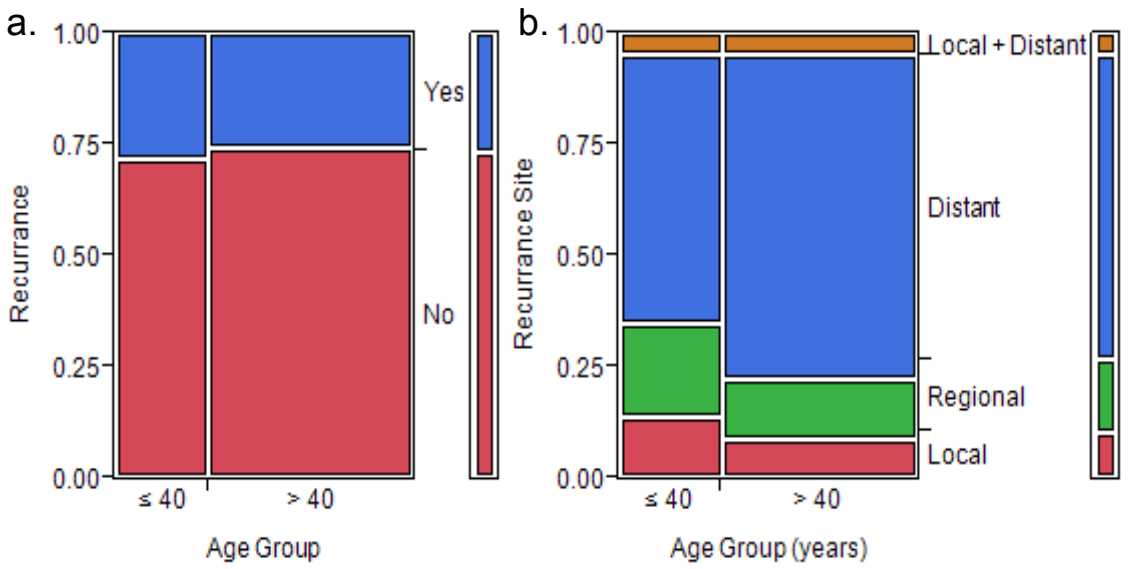

Fig. 18: Contingency plots comaring a) frequency of recurracne and b)site of recurrance across age groups

recurrence in < 40 age group is due to the higher number of APRs in the young.

6.8 Overall Survival (OS) and Disease Free Survival (DFS)

Of the 532 patients who were treated, 320 completed treatment while the remaining 212 patients defaulted with 156 of these defaulting after neoadjuvant therapy. The 5 year overall survival and the disease free survival analysis of the patients less than 40 compared to those more than 40 and also across each 10 year age groups did not assume statistical significance (Fig. 19). However there is a trend showing

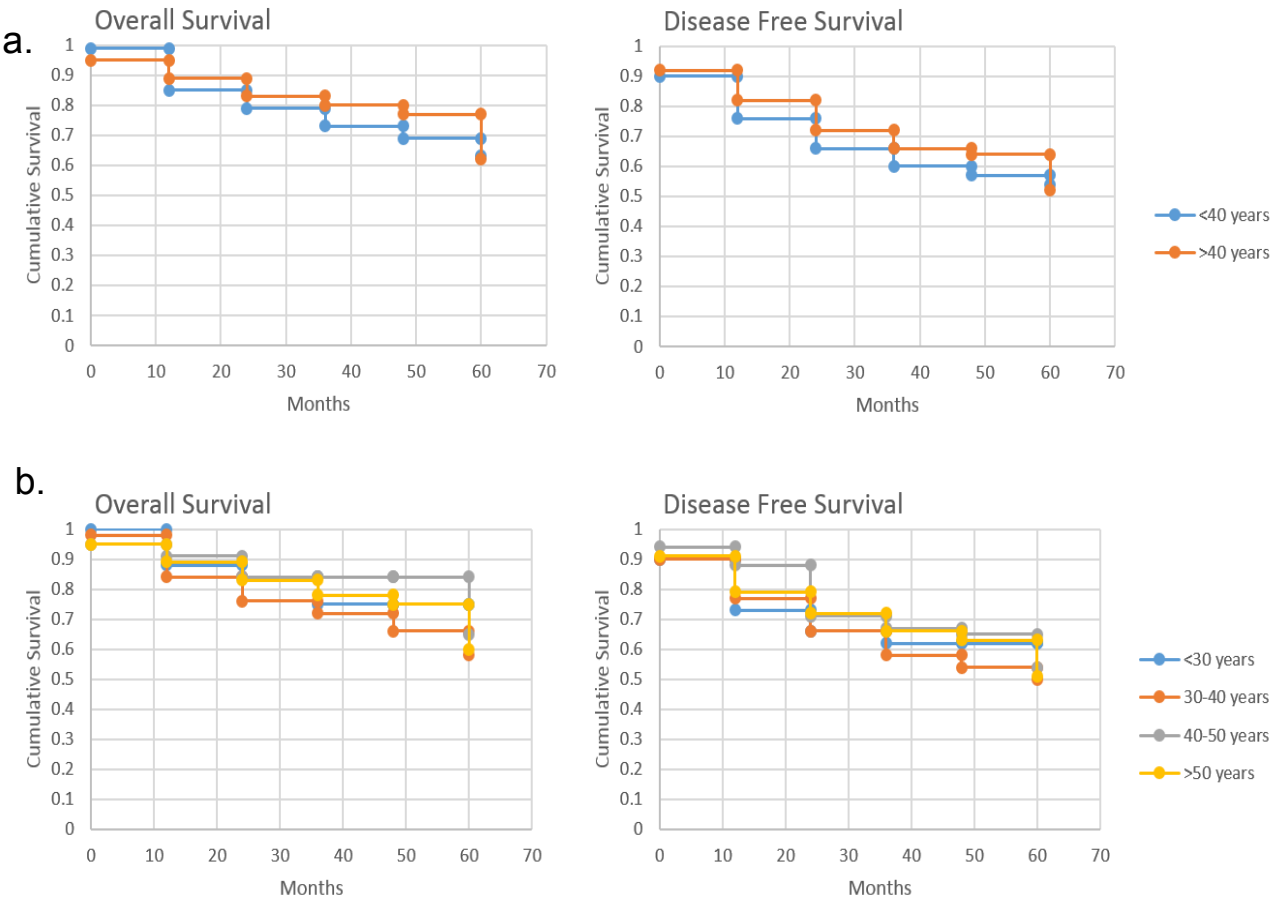

Fig. 19: Comparison of overall survial and disease free survival for patients that received complete treatment a) for patients ≤ 40 and >40 years, and b) patients in the following subcategories: < 30, 30-40, 40-50, ≥50

poorer 5 year survival (66% alive at end of 5 years) and poorer disease free survival (54% disease free at end of 5years) in the age group 30-40 compared to the rest.

This trend towards poorer OS and DFS is also seen in the less than 40 age group though not statistically significant. The only age cut off showing trend towards difference in survival was 40 years . In the

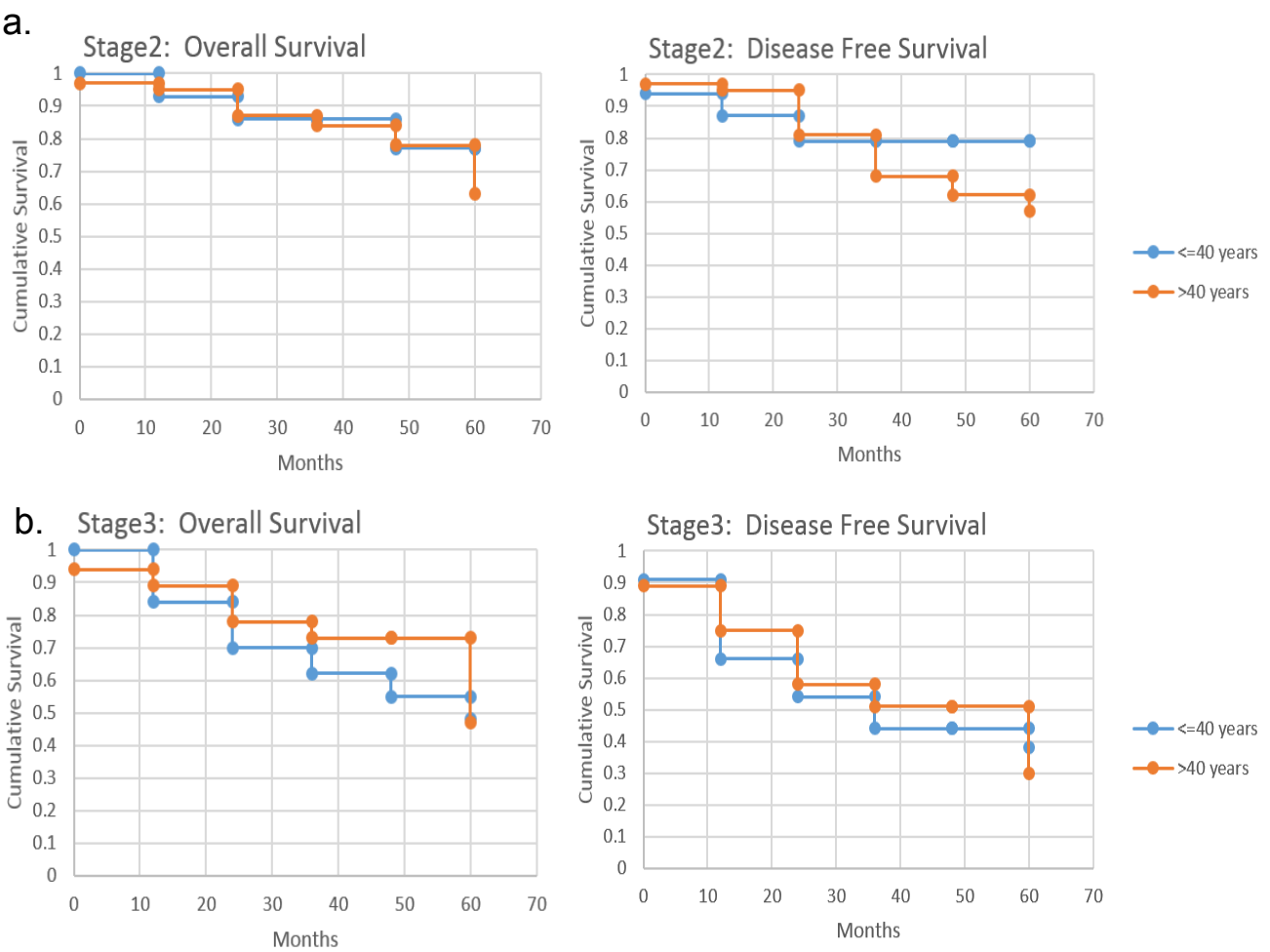

Fig. 20: Comparison of overall survial and disease free survival for a)Stage 2 and, b) Stage 3 patients that received complete treatment for patients ≤ 40 and >40 years.

other age cut offs i.e. 30, 35, 45 etc the survival patterns seemed to be similar. Further subset analysis of the 320 patients was done to compare stagewise survival separately of the 229 patients who had NACT RT followed by surgery (Fig. 20) and the 91 patients who underwent straight surgery (Fig. 21). A trend towards poorer survival was again seen in the yp stage III patients in the less than 40 age group (with 55% survivors at 5 years compared to 72% survivors at 5 years in the older group) though it did not assume statistical significance .

Again in the subset of patients who underwent straight surgery with pathological stage II disease, there was statistically significant overall

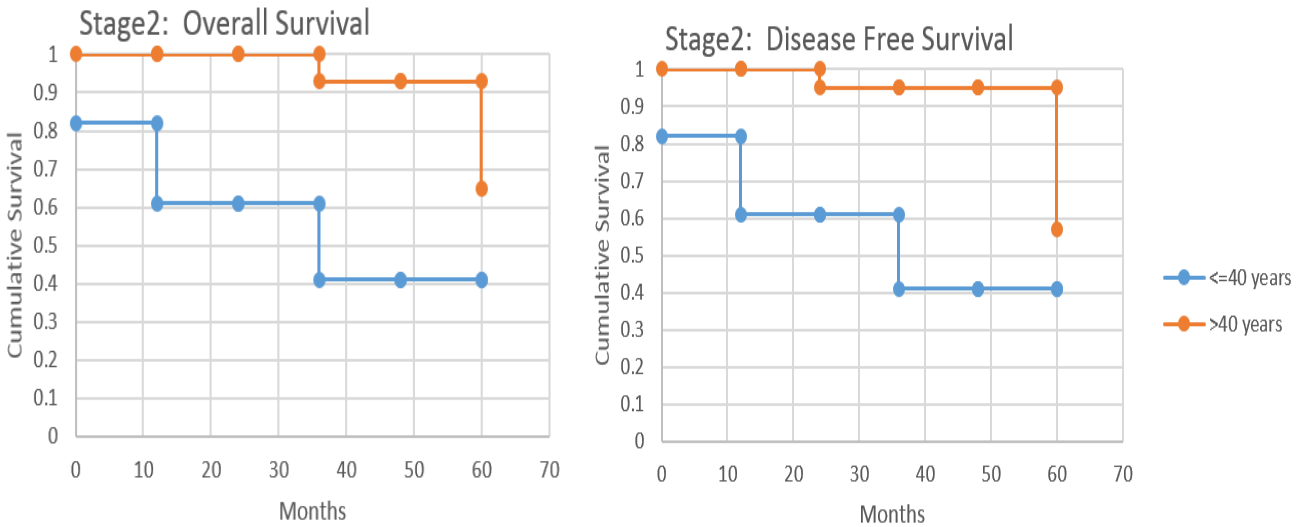

Fig. 21: Comparison of overall survial and disease free survival for Stage 2 patients that underwent direct surgery for the groups ≤ 40 and >40 years.

survival difference. But this might not be of any clinical relevance due to the low number of patients in the less than 40 age group in this subset.

Thus, if patients with distant metastasis were excluded , no statistical difference was observed in the overall survival between the younger and older patients with rectal cancer since appropriate treatment dictated by stage was delivered.

7. Discussion

The incidence of CRC among the young in Indian population is significantly higher compared to the western statistics. Our study shows that as high as 31% (41% less than 45) of the reported rectal cancer patients are younger than 40 years of age. Such higher incidences are also quoted in studies from other regional centers across India [23,24,25,27]. Further molecular and genetic studies are needed for the elucidation of novel molecular pathways in the pathogenesis of rectal cancer in younger adults as well as to identify potential new target agents for better systemic therapy for this group of patients.

Our study demonstrate that rectal cancers in the young vary significantly with respect to the histological type, grade and infiltrative pattern of growth compared to the older cohorts as witnessed in the literature [32,40,41]. The younger patients had a greater incidence of obstructive tumors requiring diversion colostomy. Thus the younger patients presented with higher clinical stage and hence more

frequently underwent neoadjuvant chemoradiation compared to the older patients.

The response to chemoradiation in the young was poorer than the old (though not statistically significant) and there was significant rates of progression of disease during treatment among the young.

The type of surgery performed was related to the distance of tumor from anal verge and more frequent sphincter sparing procedures were done in the latter half of the study period (2003-2007).

Pathological staging showed significantly higher Nodal staging among the young with a higher median nodal retrieval (10 nodes for ≤ 40 years, 7 nodes for > 40 years) and higher median positive nodes (4 positive nodes for ≤ 40 years, 3 positive nodes for > 40 years).

The overall recurrence pattern local, regional and systemic was not significantly different, but the local recurrence rated were twice more frequent in the young due to the more distal tumors , more number of APR done and advanced cT stage .

Our findings for the incidence of rectal cancer in young concur with other epidemiological studies from various regional cancer centers in

India. We therefore cannot duplicate western screening strategies that advice colonoscopy only after the age of 50 years to bring down the mortality in rectal cancer. Our emphasis, instead, should be on the early detection of rectal cancer through awareness programs among the public, and more so among the medical fraternity. There are several reasons for delayed detection of rectal cancer in younger adults.

- Ignorance in the public and the medical community about such a higher incidence of rectal cancer among the young.
- Reluctance on the part of patients to approach qualified medical professionals and attribution of symptoms to hemorrhoids by the patient and the physician
- Lack of training and reluctance among the peripheral medical professionals and health workers about the value of proper digital rectal examination to detect cancer

Educating the nonsurgical medical health professional about the importance of digital rectal examination (DRE) would do a lot towards early detection of cases. In fact, our study show that irrespective of the

age, around 80% of all rectal cancers were within 6cm from the anal verge which can be easily detected by DRE.

8. Conclusion

If familial cancer of rectum in the young are excluded, the outcome of treatment in the young is comparable to the older population. Hence the pessimism associated with young rectal cancer patients must be shed away and they should be treated as any other patient appropriate for the stage.

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